Remarks

At the outset, Applicants invite the Examiner's attention to co-pending U.S. Patent Application Serial No. 09/869,229.

Claims 1-27 are cancelled herein, without prejudice to the subject matter contained therein. New claims 28-40 have been added. Support for the new claims exists throughout the specification, for example at Example 9; Table 8; Tables 5 and 7; Table 6; Table 4; Figures 7a-7d; and Figures 8a-8d. No new matter is introduced by these amendments.

Rejections under 35 U.S.C. § 112

On page 2 of the Office Action, the Examiner rejects claims 1, 2, 18-21, and 24-27 under § 112, second paragraph, for failing to point out and distinctly claim the subject matter of the invention. Basically, the Examiner asserts that claims reciting an array comprising from 20 to about 1000 regions … selected from Table 4," is inconsistent with the 47 antibodies listed on that Table. Applicants traverse the rejection. Yet, in an effort to clarify the claims and expedite prosecution, these claims have been cancelled, mooting this rejection. Please note that new claims 28-40 do not recite the rejected language.

On page 3 of the Office Action, the Examiner rejects claims 1, 2, 18-21, and 25-27 under § 112, first paragraph, for new matter and failure to provide adequate written description. More specifically, the Examiner states that the disclosure refers to a number of regions from 7 to 1000 or 10 to 1000, but not to a number of regions from 20 to about 1000. Although, clearly, 20 to 1000 falls within the range of 7 to 1000 and 10 to 1000, these claims have been cancelled, mooting the rejection. The Examiner also rejects the claims because "the description of some 47 markers does not adequately describe the genus of cell surface markers useful for distinguishing T, B, and myeloid leukemias …." Applicants traverse the rejection, but note that the claims added in this Reply do not recite the genus of cell markers. Hence, this rejection is moot and may be withdrawn.

Next, on page 4 of the Action, the Examiner rejects claims 1, 2, 18-21, and 24-27 under § 112, first paragraph, "because the specification, while being enabling for a methods for identifying a leukemia, does not reasonable provide enablement for a method of identifying the propensity of developing a leukemia." Applicants appreciate the Examiner's affirmation that the specification is enabling for methods for identifying leukemia. Regarding methods of identifying

a propensity of developing leukemia, Applicants traverse the rejection yet note that the new claims do not address this limitation. Accordingly, this rejection is moot and may be withdrawn.

The Examiner, on page 5 of the Action, rejects claim 19 under § 112, first paragraph. Applicants traverse the rejection, but because claim 19 has been deleted this rejection is moot and may be withdrawn.

Rejections under Rejections under 35 U.S.C. § 103

On page 6 of the Action, the Examiner rejects claims 1, 2, 19, 20, 26, and 27 under 35 U.S.C. § 103 "as being unpatentable over Lanza et al (European Journal of Histochemistry, 1996,Vol. 40 suppl. 1, pp. 7-14) in view of Chang et al (Journal of Immunological Methods, 1983, Vol. 65, pp 213-233 …) and Ruiz-Arguelles et al (Cytometry, 1998, vol. 34, pp. 39-42)." Applicant respectfully traverses the rejection.

The claimed invention is drawn to a method for identifying a leukemia of T cell, B cell, or myeloid lineage in a human subject comprising the steps of providing a single assay device including a solid support having an array of immunoglobulin molecules immobilized in discrete regions on the solid support, wherein the immunoglobulins are specific for the single cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56; contacting a biological sample containing leukocytes obtained from the human subject with the assay device and allowing the leukocytes in the biological sample to bind to the immunoglobulins on the solid support via cell surface marker antigens on the leukocytes to form a pattern of binding on the array; and determining the relative scale of the pattern of binding with which the cell surface marker antigens on the leukocyte have bound to the immunoglobulins on the array, such that the relative scale of the pattern of binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in the patient.

The claimed invention thus provides a pattern that provides a diagnosis in a single, rapid test, assisting clinicians to achieve a better understanding of their patient's condition and thus provide better treatment. Since the filing of the present patent application, this approach has been applied to the analysis of over 700 patients and has proved over 90% accurate when compared to traditional techniques. Applicants' technology has been also been commercialized in Australia.

Regarding the Lanza reference, the Examiner asserts, on page 6 of the Action, that Lanza discloses 27 of the antibodies listed in the Applicant's Table 4. Lanza does not, however provide

any indication, that the six markers of claim 28 (CD3, CD4, CD8, CD14, CD19, and CD56), as opposed to any of Lanza's other twenty-one antibodies, provide as a consensus marker panel to distinguish between T cell, B cell, or myeloid lineage leukemias. Indeed, Lanza notes that "There **is a need** to standardize the panel of McAbs to be used for the characterization and classification of acute leukemias," and "it must be said that the panel of markers is only provisional, since the number of useful reagents is growing rapidly, and therefore **it is wise to wait** the conclusion of some ongoing studies **before** including some of these recently developed antibodies into a new proposed list of McAbs." *See* Lanza, page 10, first column. There are certainly several immunoglobulins included in the new dependent claims that are not mentioned at all in Lanza.

The Examiner notes that Lanza does not teach the use of an antibody array, but that is an understatement: Lanza is utterly silent regarding any solid-support based assay system and does not even hint at a single assay device having an array of immunoglobulin molecules immobilized in discrete regions on the solid support. Moreover, nothing in Lanza suggests employing the panel of six cell surface marker antigens (as in new claim 28) with the contacted leukocytes to form a pattern of binding on the array, and then determining the relative scale of the pattern of binding such that the relative pattern of binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in a patient.

Regarding Ruiz-Arguelles, the Examiner merely states that this reference "teach the flow cytometric immunophenotyping of leukemia cells," and "the relative intensity of a given antigen can be different from normal." Office Action at page 7. The Examiner completely ignores that Ruiz-Arguelles cites and then flatly ***contradicts*** Lanza, and teaches away from the claimed invention. More specifically, comparing Lanza's Table IV with Ruiz-Arguelles Tables 1 and 2, the Examiner will note the inconsistencies: certain antibodies are present while others are absent and yet others are designated as markers for inapposite diagnoses. Hence, one skilled in the art would not, and could not, combine Lanza and Ruiz-Arguelles to define the six consensus antibodies of the claimed invention would distinguish leukemia of T cell, B cell, or myeloid lineage in a patient. Indeed, regarding diagnoses, Ruiz-Arguelles instructs that "in the case where the **diagnosis** of acute leukemia is made from clinical and morphological data, **this minimum panel of 14 antibodies** will provide the necessary information for determining lineage and maturity." Ruiz-Arguelles clearly teaches away from the six consensus immunoglobulins of new claim 28. In fact, one of the claimed markers, CD14, is completely absent from Ruiz-Arguelles.

There are certainly several antibodies included in the pending dependent claims that are not mentioned at all in Ruiz-Arguelles.

The Examiner's note that that Ruiz-Arguelles classifications of "dim or bright" or "different from normal" hardly provides for and a single assay device comprising a solid array of immunoglobulins with six consensus immunoglobulins with which leukocytes may bind such that the relative scale of the pattern of binding on the array may be used to distinguish leukemia of T cell, B cell, or myeloid lineage.

Chang fails to make up for the deficiencies of Lanza and Ruiz-Arguelles. Chang notes that "**if** antibodies of relevant but distinct specificities can be prepared and purified, they can be coated on a small area of a surface and be used to analyze antigens." Yet Chang used one antibody - HLA-A2 and one type of cell, or two antibodies and two types of cells. In each instance, the antibody and cell were known to interact before the experiment, thus Chang did not provide any test of wherein a cell sample of unknown character was identified by an antibody. Chang's statement that "It is apparent that the analysis of the cell binding results would be facilitated with proper instruments," hardly provides assistance, given that such instruments were not in existence (Chang evaluated binding via "naked eye," see page 219, second full paragraph). Chang certainly does not provide for the six consensus immunoglobulins (CD3, CD4, CD8, CD14, CD19, and CD56), of claim 28, as a consensus marker panel to distinguish between T cell, B cell, or myeloid lineage leukemias.

Moveover, because Lanza and Ruiz-Arguelles are utterly silent regarding any solid-support based assay system, they fail to suggest combination with Chang. Chang never mentions the application of the technique to any diagnostic screening or in particular to characterizing leukemias, and hence would not suggest combination with Lanza and/or Ruiz-Arguelles. Indeed, the publication of Chang in 1983 supports the conclusion that the claimed invention answered a long felt need to bring this type of approach to useful, commercial application for the identification of leukemias.

Hence, this § 103 rejection is inadequately supported by the cited references. Applicants respectfully request that it be withdrawn.

On page 8 of the Office Action, the Examiner rejects claims 1, 2, 19-20, 24- 26, 27, and 40 under 35 U.S.C. § 103 "as being unpatentable over Lanza et al in view of Chang and

Ruiz-Arguelles … and further in view of Stewart et al. (Cytometry, 1997, Vol. 30, pp. 231-235)." Applicants respectfully traverse the rejection.

The deficiencies of Lanza, Chang, and Ruiz-Arguelles have been discussed. Stewart does not make up for these deficiencies. Stewart refers to "panels" of antibodies that might be used for diagnostic purposes: "A 'panel' of antibodies refers to a set of tubes each containing different antibody combinations." Page 231, second column. Stewart provides a "list of antigens that are considered useful for the evaluation of particular diseases according to sample site. They are further classified as "core" and "supplemental," the former being most important for the analysis of the particular disease …" The "core" antigens to which Stewart refers to comprises twelve markers, only two of which overlap with the consensus six of claim 28. Moreover, two markers more are entirely excluded from both the leukemia core and supplemental identification lists. *See* Table 2, page 233. Importantly, Stewart refers to the inclusion of such markers in panels, the lists "do not specify how the regents are to be combined." Page 234, first column. Moreover, Stewart states that "it was clear from … discussions among all conference participants that **recommending a universal strategy for the selection of antibodies applicable to the analysis of hematologic neoplasma is unrealistic and that a consensus in this regard will be extremely difficult to reach**."

Stewart clearly fails, as do the previously cited references, to teach or suggest the consensus immunoglobulins of claim 28, most of which are completely lacking from the Stewart-proposed "core" diagnostic. Furthermore, Stewart contradicts both Lanza and Ruiz-Aguelles, providing even more confusion regarding the markers for diagnosis. Moreover, although some of the CD markers of Stewart are present in the pending dependent claims, many are absent from Stewart. Stewart also includes markers that are not present in the dependent claims, with no teaching in either regard. Indeed, combining the cited references fails to provide a "combinati[on of] previously known elements." *KSR Int'l. Co v. Teleflex Inc.*, No. 04-1350 (April 30, 2007) at 14, 15.

Stewart actually supports the patentability of the claimed invention in several ways. It signifies the long felt need, or problem to be overcome, of selecting and mixing various antibodies in tubes: the claimed invention allows for all antibodies of interest to be placed on a single assay device, for a single, rapid, and determinative test. Alternative FACS analysis was (and remains) expensive and cumbersome, such that perhaps ten to twelve markers could be

tested, and not in a single assay device. Stewart articulates the long felt need or problem to be overcome, noting the extreme difficulty in providing for a consensus regarding the selection of antibodies: the claimed invention provides for that. Hence, Applicants request that this § 103 rejection be withdrawn.

Also on page 8 of the Office Action, the Examiner rejects claims 1, 2, 18-20, and 26 under 35 U.S.C. § 103 "as being unpatentable over Lanza et al and Chang and Ruiz-Arguelles … and further in view of Paul (Fundamental Immunology, Third Edition, 1993, page 460). Applicants respectfully traverse the rejection.

The Examiner states that "Paul teaches that polyclonal antibodies have advantages over monoclonal antibodies …" This may be so, but because the previously cited references do not teach or suggest the claimed method for identifying a leukemia of T cell, B cell, or myeloid lineage in a human subject comprising the steps of providing a single assay device including a solid support having an array of immunoglobulin molecules immobilized in discrete regions on the solid support, wherein the immunoglobulins are specific for the single cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56; contacting a biological sample containing leukocytes obtained from the human subject with the assay device and allowing the leukocytes in the biological sample to bind to the immunoglobulins on the solid support via cell surface marker antigens on the leukocytes thus forming a pattern of binding on the array; and determining the relative scale of the pattern of binding with which the cell surface marker antigens on the leukocyte have bound to the immunoglobulins on the array, such that the relative scale of the pattern of binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in the patient, that Paul refers to polyclonal antibodies can not over come those deficiencies. Hence, Applicants requests that this § 103 rejection be withdrawn.

In addition to answering a long felt need, as noted above, the Applicants also invite the Examiner to consider additional "secondary factors" which support the patentability of the claimed invention over the prior art. Applicants invite the Examiner's attention to the MEDSAIC press release submitted herewith. This reports that Applicants' licensee received the 2005 "BioFirst Commercialisation Award" for outstanding achievement in technology for its leukemia and lymphoma diagnostic. In addition to the recognition of commercial development and success in Australia, MEDSAIC was deemed most likely to achieve international success with its

technology. This award evidences the recognition of others and commercial success of the claimed invention.

Applicants also provide for the Examiner a recent, pier-reviewed article validating the Applicants application of the instant technology: Belov et al., "Analysis of Human Leukemias and Lymphomas Using Extensive Immunophenotypes from an Antibody Microarray," 135 British Journal of Haematology, 134-97 (2006). In this article, the claimed invention provided for a single assay device in which 82 markers could be studied simultaneously. Over 700 patients were profiled and the levels of consensus for classification using standard criteria were more than 90% accurate. This paper clearly evidences the improvement over any of the techniques addressed in the art cited by the Examiner.

In summary, comparing all of the cited references, in combination, to the claimed invention, it is clear that claimed invention reflects an advancement and "real innovation." *KSR Int'l. Co v. Teleflex Inc*., No. 04-1350 (April 30, 2007) at 15.

Conclusion

Applicants respectfully request reconsideration of this application and allowance of the pending claims in view of the above remarks.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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